Indian Journal of Chemistry
Vol.36B, July 1997, pp.541 - 544

Rapid Communication

A novel one-pot synthesis of 4-chloro-3-quinolinecarboxaldehydes, 4-chloroquinolines and 4-chloro-3-ethylquinolines using Vilsmeier reagent

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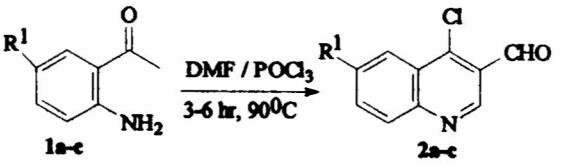
Received 11 June 1997; accepted 30 June 1997

Various substituted 1-(2-aminophenyl)ethanones on treatment with Vilsmeier reagent at 90°C for 3-6 hr yield 4-chloro-3-quinolinecarboxaldehydes. Whereas substituted N-[2-(1- oxoethyl) phenyl] acetamides afford both 4-chloroquinolines and 4-chloro-3-quinolinecarboxaldehydes. However, in the case of substituted 1-(2-aminophenyl)butanones and N-[2-(1-oxopropyl) phenyl] acetamides, only 4-chloro-3-ethylquinolines are obtained.

Quinolines[1] constitute an important class of heterocyclic molecules. Various substituted quinolines are reported to possess a wide range of biological activities including antimicrobial[2a], antitumor[2b], anticonvulsant[2c], antidepressant[2d], antimalaria[2e], antihistamine[2f], etc. Recently, various substituted quinolines have been prepared by samarium iodide mediated[3a], zirconium promoted[3b], mercury controlled cyclization[3c], and 3-component coupling reactions[3d,3e]. The other methods for the synthesis of quinoline derivatives are photocyclization[3f] and radical cyclization[3g].

Vilsmeier-Haack-Arnold reagent (chloromethyleniminium salts) is extensively used for formylation[4] of activated aromatic, heteroaromatic and carbonyl compounds. The synthesis of various heterocyclic compounds[5] can also be achieved by Vilsmeier reagent. Recently, some interesting cyclization reactions under Vilsmeier condition have been reported from this laboratory[6]. In continuation of our interest in this versatile reagent, we wish to report here that the reaction of substituted 1-(2-aminophenyl)ethanones **1** with $DMF/POCl_3$ for 3-6 hr at 90 C affords the substituted 4-chloro-3- quinolinecarboxaldehydes 2 (Scheme I) in good yields (Table I).



1a-c **2a-c**

Scheme I

Table I — Reaction products of 1-(2-aminophenyl)-ethanones **1** with Vilsmeier reagent

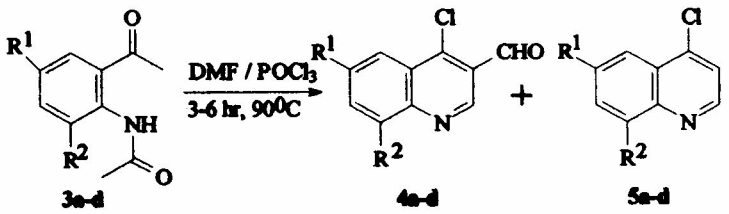
Entry	1,2	R^1	Yield of **2** (%)[a,b]
1	**a**	H	43
2	**b**	Br	66
3	**c**	Cl	60

[a] All the compounds gave satisfactory spectral data.
[b] Yields reported here are after separation from flash chromatography.

The above methodology was successfully extended to the synthesis of various substituted 4-chloro-3-ethylquinolines **7** from 1-(2-aminophenyl) butanone and its acetyl derivatives **6**. According to this procedure, the 1-(2-aminophenyl) butanone **6a** and acetamides **6b-d** were treated with Vilsmeteir reagent at 90°C for **3-5** hr to yield **4**-chloro-3-ethylquinolines **7** (Scheme III) as the only products generally in excellent yields (Table III).

Although few reports are available for the synthesis of quinolinecarboxaldehydes[7] using Vilsmeier reagent, the regioisomer, 4-chloro-3-quinolinecarboxaldehydes, has never been synthesized either using Vilsmeier reagent or by any other method. This is the first method for the synthesis of 4-chloro-3-quinolinecarboxaldehydes from 1-(2-aminophenyl)ethanones.

Further, we were interested to extend the scope of this reaction by the introduction of acetyl group on nitrogen atom. Thus, substituted N-[2(1-oxoethyl) phenyl]acetamides **3** on treatment with Vilsmeier reagent at 90 C afford not only 4- chloro-3-quinolinecarboxaldehydes **4** but also 4-chloroquinolines **5** (Scheme II) in good yield (Table II).



Scheme II

Table II — Reaction products of N-[2(1- oxoethyl)-phenyl]acetamides with Vilsmeier reagent

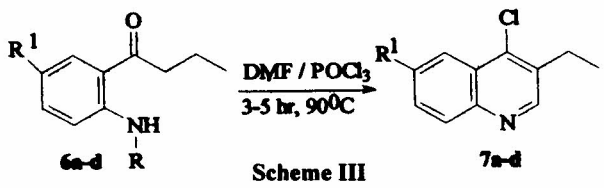
Entry	3,4,5	R^1	R^2	Yield (%)[a,b] 4	5
1	a	H	H	60	14
2	b	Br	H	74	8
3	c	NO_2	H	87	-
4	d	H	NO_2	24	17

[a] All the compounds gave satisfactory spectral data.
[b] Yields reported here are after separation from chromatography.

Table III — Reaction products of 1-(2-aminophenyl)-butanone **6a** and N-[2(1-oxopropylphenyl]acetamides **6b-d** with Vilsmeier reagent

Entry	6,7	R	R^1	Yield of 7 (%)[a,b]
1	a	H	H	38
2	b	$COCH_3$	H	81
3	c	$COCH_3$	Br	79
4	d	$COCH_3$	NO_2	86

[a] All the compounds gave satisfactory spectral data.
[b] Yields reported here are after separation from chromatography.

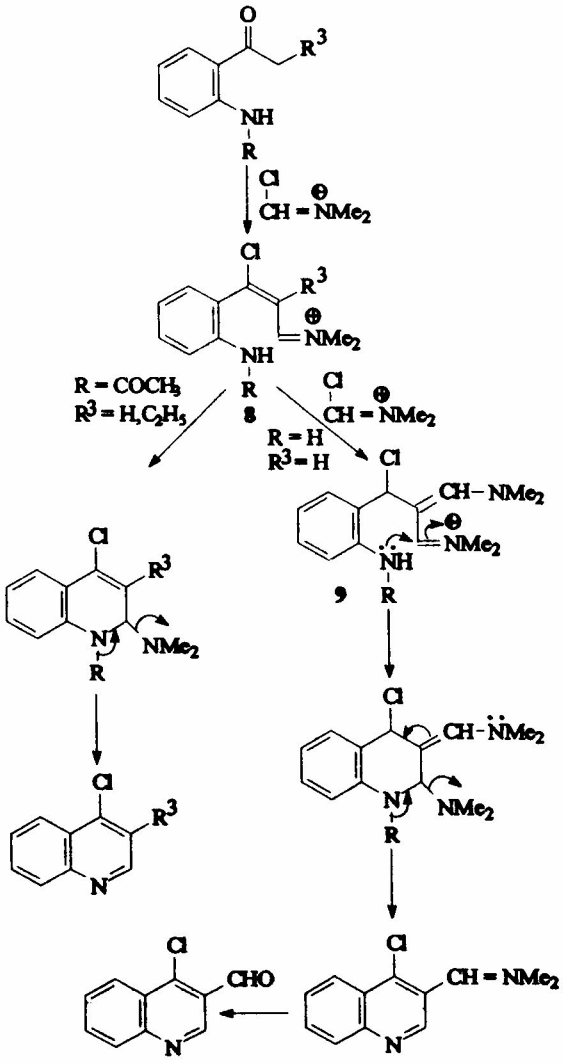


Scheme III

The reaction shown in Scheme II proceeds quite contrary to the expected cyclization *ortho* to acetamido group. In the case of *p*- nitro derivative **3c**, quinoline alone was obtained and not quinolinecarboxaldehyde.

The above results suggest that the protection of N-acetyl derivatives improves the yields drastically. This may be due to the prevention of N-methyleneiminium salt formation.

Although it is premature to propose a detailed mechanism at this stage, based on the above results a plausible mechanism can be proposed for this reaction (cf. Scheme IV). Chloromethyleniminium salt formed ffrom DMF and $POCl_3$ reacts with 1-(2-aminophenyl) ethanones to yield the



Scheme IV

monomethyleniminium salt **8**. From **8** the reaction proceeds in two different routes. The salt **8** reacts with another molecule of chloromethyleniminium salt to yield the dimethyleniminium salt **9** which undergoes cyclization leading to **2** in the case of 1-(2-aminophenyl)ethanones. However, in the case of acetamide derivatives a major portion of the compound forms the monomethyleniminium salt **8** which undergoes cyclization to yield **4**. A small portion of the compound gets hydrolysed to the corresponding 1-(2-aminophenyl)ethanones which are then cyclized to **2** as mentioned above. However, quite unexpectedly, 2-aminobutyrophenone and its acetyl derivatives yielded only monomethyleniminium salt **8** which undergoes cyclization to yield **7**.

In conclusion, a simple and convenient synthesis of various substituted 4-chloro-3-quinolinecarboxaldehydes, 4-chloroquinolines and 4-chloro-3-ethylquinolines has been achieved by Vilsmeier reagent. The synthesis of some other derivatives is to be communicated shortly.

Experimental Section

Preparation of 4,6-dichloro-3-quinolinecarboxaldehyde 2c. To a stirred solution of 1-(2-amino-5-chlorophenyl)ethanone (0.5 g, 0.0029 mole) in DMF (1.73 g, 0.0236 mole) cooled to 0 C, $POCl_3$ (1.81g, 0.011 mole) was added dropwise over 30 min. The reaction mixture was stirred at room temperature for 1 hr and maintained at 90 for 4½ hr. The resulting mixture was neutralized with crushed ice containing sodium acetate and left overnight. The separated solid was filtered and purified by passing through a flash column (9:1 pet. ether-ethyl acetate) to yield **2c** in 60% yield, m.p. 228-30 (dec); MS: m/z 225 (M^+), 227 (M^++2) 229 (M+4); IR(KBr): 1690, 765 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): 10.65 (s, 1H, CHO), 9.20 (s, 1H), 8.32(s,1H), 8.06-8.03(d, 1H, *J*=9Hz), 7.71-7.69(d, 1H, *J*=6Hz); ^{13}C NMR (75MHz, $CDCl_3$): 188.6, 149.1, 148.7, 147.1, 135.0, 133.9, 131.7, 126.4, 124.7, 123.9.

Preparation of 4-chloro-3-ethylquinoline 7a. To a stirred solution of N-[2-(1-oxopropyl)phenylacetamide (0.82 g, 0.004 mole) in DMF (3.5 g, 0.048 mole) cooled to 0 C, $POCl_3$ (4.9 g, 0.032 mole) was added dropwise over 30 min. The reaction mixture was stirred at room temperature for 1 hr and maintained at 90 C for 5 hr. The workup, simillar to above, yielded **7a** in 81 % yield; MS: m/z 191 (M^+), 193 (M+2); IR (KBr): 820 cm^{-1}, ^1H NMR (300MHz, $CDCl_3$): 8.67 (s, 1H), 8.14-8.11 (d, 1H, *J*=9Hz), 8.03-8.00 (d, 1H, *J*=9Hz), 7.64-7.59 (m, 1H), 7.54-7.51 (m, 1H), 2.91-2.83(q, 2H), 1.27-1.24(t, 2H); ^{13}C NMR (75MHz, $CDCl_3$): 151.2, 147.3, 140.1, 134.0, 129.3, 128.9, 127.2, 126.2, 123.7, 24.7, 13.9.

Acknowledgement

One of the authors (R R A) is grateful to UGC and CSIR, New Delhi for a fellowship.

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